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SPECIAL ARTICLE

Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition

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Specific criteria have been established to define the occurrence of myocardial infarction (MI) and stroke in cardiovascular clinical trials, but there is not a consistent definition for heart failure. Heart failure events appear to occur at a rate that is similar to stroke and MI in trials of hypertension, hyperlipidaemia, diabetes, and coronary heart disease, yet a consistent approach to defining heart failure events has not yet been realized. The wide range of definitions used in clinical trials makes it difficult to interpret new data in the context of existing literature. This inconsistency has led to challenges in determining the incidence of heart failure in cardiovascular studies and the effects of interventions on these endpoints. This paper examines issues related to defining heart failure events in cardiovascular clinical trials and presents a definition to formally address this issue.

Keywords Cardiovascular disease • Heart failure • Clinical trials • Hypertension • Hypercholesterolaemia

Background and scope of the problem

Criteria have been established to define the occurrence of myocardial infarction (MI) or stroke in cardiovascular clinical trials, but a consensus definition has not been reached for heart failure events.[1–3] In December 2005, a group of cardiovascular clinical trialists, biostatisticians, National Institutes of Health (NIH) scientists, regulators, and pharmaceutical industry scientists met to discuss current issues related to cardiovascular clinical trials. This manuscript summarizes the group's discussion on the methodology of defining heart failure events in cardiovascular trials.

Overview of heart failure definitions

The definition of heart failure events varies widely across the spectrum of cardiovascular clinical trials (see Supplementary material online, *Table S1*). Specific definitions are not provided in many publications (even though they may be defined in the trial protocol), and this practice prevents the reader from gaining a full understanding of the heart failure event. Majority of cardiovascular trials has used endpoint committees to adjudicate events using prespecified definitions (see Supplementary material online, *Table S1*).

Significance of heart failure events relative to stroke and myocardial infarction

A review of published clinical trials in various cardiovascular conditions shows that the incidence of heart failure is highly variable, possibly because of varying definitions as well as differing risk of the population under study. In general, the incidence of heart failure is similar to that of other important endpoints that do have established event criteria, such as stroke and MI (see

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Supplementary material online, *Table S2*). This observation is consistent across the spectrum of cardiovascular studies.[4–8]

The accurate recognition of heart failure events is important because of the poor outcomes associated with heart failure.[9–13] Heart failure as a clinical event is important to detect, not only because of its associated morbidity and mortality, but also because of its societal burden.[14]

Heart failure events may reflect myocardial injury and/or pathophysiologic progression. The altered haemodynamics, elevated neurohormones, and increased filling pressures that occur in the setting of worsening heart failure may lead to myocardial injury or necrosis.[15] Several studies have reported troponin release in patients hospitalized for worsening heart failure, which may reflect myocardial damage leading to worsening, or alternatively, myocardial damage due to the exacerbation of heart failure.[16–26] Although most patients improve symptomatically and survive to hospital discharge, the episode suggests that such patients may be functioning near the limits of their cardiovascular reserve and that they are prone to further episodes and an adverse outcome. Prior heart failure hospitalization predicts all cause mortality.[27] Thus, correctly identifying heart failure events may aid in subsequent risk stratification.

Occurrence of heart failure events in non-heart failure clinical trials

Heart failure events have been reported in many hypertension trials, and the rate is similar to or higher than that for stroke and MI in most of these studies (see Supplementary material online, *Table S2*). In comparison to the hypertension literature, fewer lipid lowering trials have reported the incidence of heart failure events (see Supplementary material online, *Table S2*). However, when reported, heart failure event rates were similar to, and in some studies higher than, stroke rates. In general, the rate of coronary heart disease or MI was higher than heart failure.

Heart failure events are especially important to evaluate in diabetes trials because of the potential for diabetes treatments to cause or exacerbate heart failure, and because diabetes is a risk factor for heart failure development.[28,29] For example, in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, the rate of heart failure appeared to be higher than either stroke or non-fatal MI over 34.5 months of follow-up.[30] The incidence of heart failure hospitalization in coronary heart disease clinical trials is also similar to the incidence of stroke and MI (see Supplementary material online, *Table S2*).

Occurrence of heart failure events in heart failure clinical trials

Not surprisingly, worsening of or hospitalization for heart failure is a frequent event in clinical trials of patients with heart failure, whereas MI and stroke account for a smaller proportion of events (see Supplementary material online, *Table S2*). This observation may be due to the fact that patients do not survive long enough after a heart failure diagnosis to experience MI or stroke events, yet hospitalizations for heart failure are quite common. Another potential explanation may be that patients with heart failure are possibly more likely to die suddenly from MI and stroke than to experience these events as non-fatal outcomes.[31]

The observation that heart failure events occur with a much higher frequency than stroke or MI events is consistent across chronic heart failure studies (see Supplementary material online, *Table S2*). However, the definition used to classify heart failure events differs across trials (see Supplementary material online, *Table S1*), as does the process to confirm the event classification. In heart failure trials, hospitalization is generally used to identify the event, although in some cases administered treatments or change in therapy are also used. The differences in these definitions contribute to difficulties in data interpretation.

Occurrence of heart failure events in observational studies

The incidence of heart failure is also similar to the incidence of stroke or MI in observational studies. The age adjusted biennial rate of heart failure per 1000 was 13.9, and the age adjusted rate of stroke was 12.4 among hypertensive men in the Framingham Heart Study.[32] The Cardiovascular Health Study reported a heart failure incidence of 19.3 per 1000 person years; the rate of first hospitalized MI or coronary heart disease death was 19.2 events per 1000 person years.[33]

The influence of therapy on heart failure events in cardiovascular non-heart failure clinical trials

Importantly, heart failure events are modifiable with drug therapy even in populations in which heart failure has not been previously identified. In addition, the extent to which heart failure risk can be lowered is comparable to risk reductions of other important endpoints such as MI or stroke (see Supplementary material online, *Table S2*). Thus, accurately defining heart failure events is also relevant from the standpoint of initiating effective treatment options.

Hypertension

ACE-inhibitors and angiotensin receptor blockers (ARBs) were associated with a significant reduction in heart failure events as compared to placebo in a meta-analysis of 29 hypertension trials representing 162 341 subjects (*Figure 1A* and *B*).[34] A non-significant trend towards the increased heart failure events was observed with the calcium channel antagonist vs. placebo comparison (*Figure 1A*).[34] Similar findings were observed in the ALLHAT study, where amlodipine was associated with a greater heart failure risk as compared to chlorthalidone.[35] Lisinopril was associated with a greater heart failure risk as compared to chlorthalidone during 1 year, but there were no differences between chlorthalidone and lisinopril during subsequent years, whereas the risk associated with amlodipine persisted.

The mechanism of action supporting these observed effects on heart failure events is not known. The Blood Pressure Lowering

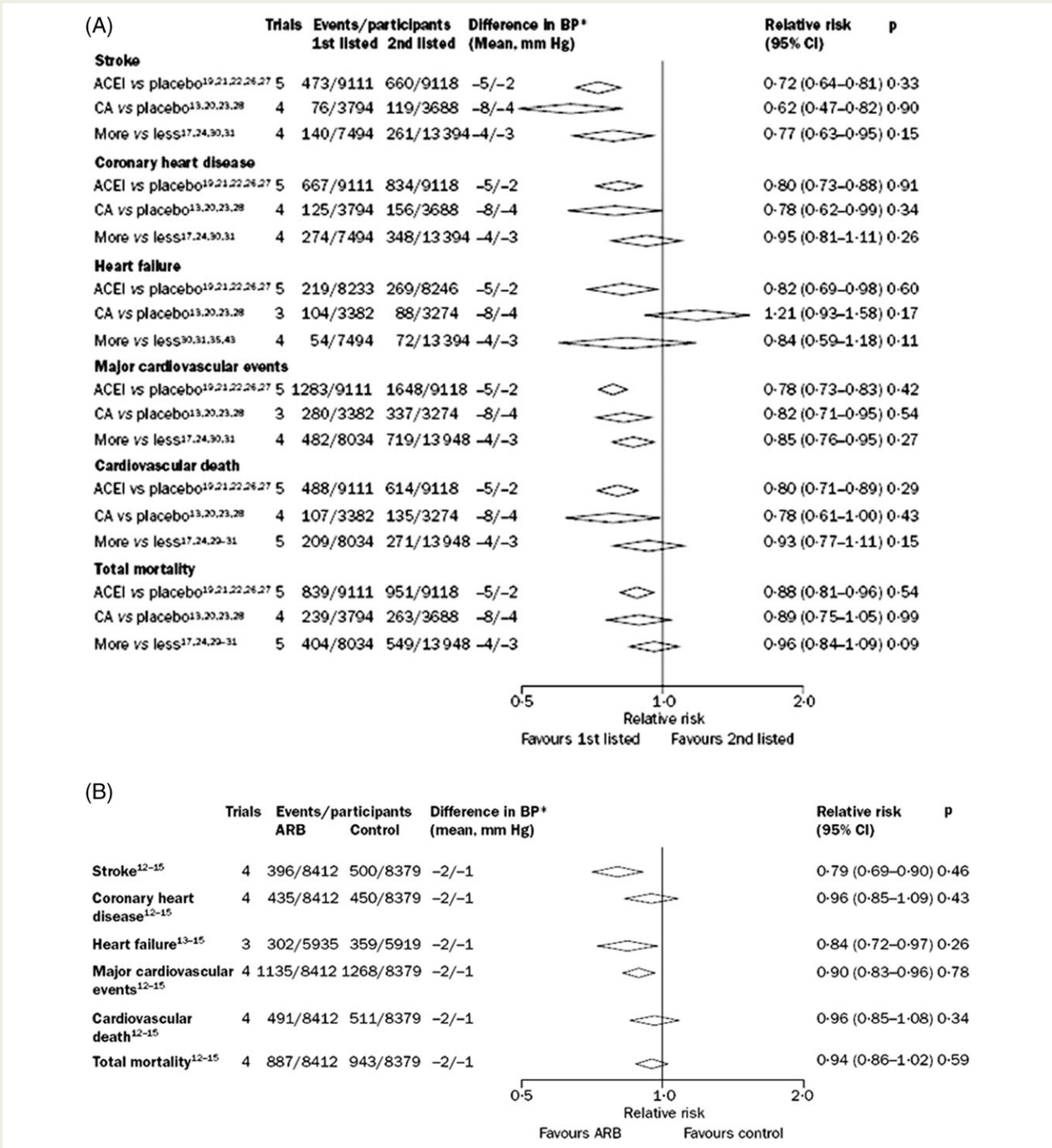

Figure 1 (*A*) Effect of drug Therapy on Cardiovascular Outcomes in the Blood Pressure Lowering Treatment Trialists' Collaboration Meta-Analysis. Reprinted with permission from ref. 34. (*B*) Effect of ARBs on Cardiovascular Outcomes in the Blood Pressure Lowering Treatment Trialists' Collaboration Meta-Analysis. Reprinted with permission from ref. 34.

Treatment Trialists' Collaboration meta-analysis found a predictable and direct association between blood pressure reduction and stroke, coronary heart disease, major cardiovascular events, cardiovascular death, and total mortality. However, heart failure events were not related to the changes in blood pressure.[34] This observation raises the hypothesis that blood pressure may be an appropriate surrogate marker of MI and stroke events, but it may not adequately predict heart failure events. Another possible explanation for the lack of an observed relationship between blood pressure lowering and heart failure events may be that the inconsistent definitions used for heart failure among hypertension trials decreased the ability to detect such an association.

Hyperlipidaemia

Reductions in heart failure events have also been observed in statin trials (see Supplementary material online, *Table S2*). The findings of these analyses have led to interest in exploring statins as potential therapy for heart failure.[36,37] For example, a reduction in heart failure hospitalizations was reported in the Treating to New Targets (TNT) study (HR 0.74, 95% CI 0.59–0.94; $P = 0.01$). Significant reductions in cerebrovascular events (HR 0.77) and major coronary heart events (HR 0.80) were also observed.[38]

Heart failure as an adverse event

Accurately defining heart failure is important not only for detecting signals of treatment efficacy, but also for identifying potential safety issues. Some cardiovascular studies have detected an association between pharmacologic therapy and heart failure risk. Both doxazosin and amlodipine were associated with higher rates of heart failure in ALLHAT when compared to diuretics and ACE inhibitors.[39,40] The observation of increased heart failure events in the doxazosin arm prompted early discontinuation of that study arm.[40] In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, the relative risk for HF events was higher with amlodipine as compared to valsartan.[41] These findings have stimulated some debate on whether the events detected in these trials were heart failure, or if they were confounded by diuretic withdrawal in ALLHAT or peripheral edema side effects associated with amlodipine. These examples illustrate the challenges clinical researchers face because of the lack of a standard heart failure definition.

Similar concerns were evident with pioglitazone in The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial.[30] In the PROactive study, a lower combined rate of death, MI, acute coronary syndrome, stroke, cardiac intervention, leg amputation, or leg revascularization was observed for pioglitazone treated patients as compared to placebo.[30] However, the rate of any reported heart failure was higher (see Supplementary material online, *Table S2*).[30] In this study, heart failure events were determined by the investigator, and non-fatal events were not adjudicated. Edema in the absence of heart failure was also higher in pioglitazone treated patients (21.6 vs. 13%). Loop diuretics were added in 7.7% of pioglitazone patients and 5.4% of placebo patients. It is possible that some of the non-adjudicated heart failure events could have been edema without heart failure. To address this concern, Ryden *et al.* conducted a post hoc, blinded, independent adjudication of investigator reported serious heart failure events, which confirmed the investigator reported findings.[42] As illustrated by each of these studies, the true presence of heart failure is difficult to assess without concrete definitions or evidence of structural myocardial changes consistent with heart failure.

Criteria for a heart failure event

Event definitions in non-heart failure studies

A major problem of defining new-onset heart failure in trials is the lack of a robust method to identify when breathlessness or ankle swelling is due to heart failure or another cause. The need for hospitalization or administration of intravenous medications may be adequate to capture more severe heart failure events and is useful as evidence of exacerbation of the underlying disease in trials of heart failure, but in low risk, primary prevention populations, objective criteria of myocardial dysfunction is probably necessary to confirm a new heart failure diagnosis, as is clear in diagnostic guidelines.[43] For example, objective measures of cardiac dysfunction in the PROactive trial may have helped to determine whether ankle edema was due to the localized collection of fluid or really reflected heart failure.[30] However, assessments such as echocardiography are costly and would not be feasible in most large clinical trials. BNP may also be a useful diagnostic tool to establish or refute the occurrence of a heart failure event. BNP would serve as a less expensive measure than echocardiography or other assessments of myocardial structure. In conjunction with symptoms, BNP is associated with high sensitivity and specificity for heart failure.[44] Either BNP or NT-proBNP could be used; however, BNP may be a less complicated measure than NT-proBNP, since the cutoffs for NT-proBNP vary with age (see Supplementary material online, *Table S3*).[45,46] If *de novo* HF is to be ascertained, the criteria used, whether echocardiography, BNP, or other objective assessments, should be contrasted against normal baseline measures.

The sensitivity (proportion of true positives) and specificity (proportion of true negatives) to detect heart failure events differs according to how the event is defined. Investigator ascertainment is likely associated with a moderately high sensitivity, but relatively low specificity. Investigators may be likely to detect heart failure when it exists, but they are less able to differentiate correctly between true heart failure and a clinical situation that is suspicious but actually negative for heart failure. The definition that combines signs and symptoms with direct (echocardiography) or indirect (BNP) evidence of cardiac dysfunction is likely to produce the greatest sensitivity and specificity.

In some cases, an adjudication committee, blinded to trial treatment assignment, may be necessary to establish the heart failure diagnosis. Adjudication committees apply systematic criteria to events, which may be important particularly for events such as heart failure where uniform criteria are lacking. In the Cardiovascular Health Study, the investigators initially classified all events, and a rigorous adjudication process followed.[47–49] The agreement between the initial and adjudicated assessment was the greatest for MI and stroke endpoints (86.1 and 91.8%, respectively).[47] The concurrence between the initial and adjudicated assessment for heart failure was lower at 70.4%, illustrating the challenges investigators face with classifying heart failure events when a specific, uniform definition is lacking. In ALLHAT, there was 83% agreement on a subset of heart failure hospitalization events between the adjudication committee and site investigators.[40] However, in the INSIGHT trial, 114 events were considered heart failure by the investigator while the CEC identified only 50 events that met heart failure criteria, a 56% reduction from the investigator assessment.[50] In the recent analysis of the PROactive study, investigator reported and adjudicated events were quite similar, with investigators reporting a heart failure hospitalization rate of 5.7 and 4.1% in the pioglitazone and placebo groups,

respectively. The adjudicated heart failure hospitalization rate was 5.5 and 4.2%.[42]

A consistent definition would ensure that heart failure events in non-heart failure trials are accurately reported and that outcomes can be interpreted across heart failure trials. Both the presence of heart failure and treatment for heart failure should be documented. Several criteria should be required for an event to be classified as heart failure. For a non-heart failure trial, it may also be important to distinguish among patients with a pre-existing heart failure substrate vs. those without. The PROactive example is useful to further illustrate this concept.[30] These study results cause one to question whether the volume overload associated with pioglitazone was sufficient to cause heart failure in a patient with a normal heart, or if the development of heart failure was limited to those patients who had an abnormal cardiac substrate such that the volume overload produced by pioglitazone caused symptoms of heart failure. This distinction may be useful to accurately define and characterize the event. The definition should also be clinically meaningful. Death due to heart failure is an important event, but heart failure hospitalization or functional incapacity is equally important in reporting trial results. Beyond these basic requirements, several methods to define heart failure events have been used.

Heart failure hospitalization

Hospital admission is the main factor used by many clinical trials to define heart failure events. Hospitalization is a more objective outcome as compared to signs and symptoms. In addition, it is clinically significant since it is associated with poor prognosis. However, several difficulties are associated with using hospitalization alone as a criterion. First, the hospitalization threshold differs across institutions and regions of the world, and this may account for some of the variability in reported events. Second, some patients with a previous diagnosis of heart failure who develop worsening heart failure symptoms will be managed as outpatients in disease management programs. Other patients who lack access to such intensive monitoring and care programs may be hospitalized for identical symptoms. These practice pattern variations may confound the results of clinical trials that rely on hospital admissions to define heart failure events, particularly in international trials, where differences in patterns of care may be particularly evident.

Treatment requirements to establish heart failure

The administration of intravenous therapy for heart failure is also used to identify heart failure events. However, this requirement is problematic for similar reasons. Practice patterns for prescribing intravenous diuretics, vasodilators, or inotropes differ across institutions and countries. European physicians tend to use intravenous diuretics less often than physicians in the USA. Conversely, investigators in the USA are less likely to use intravenous inotropes than their European colleagues, although this observation may be related to the clinical characteristics and severity of the heart failure presentation.[9,12,51–53] Thus, using intravenous therapies as a mechanism to define heart failure events is challenging because whether or not a patient meets the definition may be dependent on factors not directly related to the patient's clinical condition, such as local practice patterns.

Reporting of fatal and non-fatal heart failure events

Both fatal and non-fatal heart failure events are important to ascertain in clinical trials, but these distinctions are inconsistently reported in published papers.[54] It is important to ascertain the number of patients with heart failure, MI, or stroke events and subsequently classify these events according to whether the patient did or did not survive over a given time period. Heart failure death is often not distinguished from all cause or cardiovascular mortality. Thus, it is difficult to determine the breakdown of fatal and non-fatal heart failure events in clinical trial reports. Of the non-heart failure cardiovascular trials reporting such data, the proportion of patients experiencing a fatal event attributed to heart failure is quite low in comparison to the non-fatal heart failure events.[55–57]

Fatal heart failure events occur at a higher rate in heart failure trials than in non-heart failure cardiovascular trials, but the non-fatal event rate is still generally several fold higher than the fatal event rates.[58,59] Fatal heart failure events occur at a higher rate in more severe heart failure populations, such as that studied in the Randomized Aldactone Evaluation Study (RALES).[60]

Within the context of fatal heart failure events, mode of death may be important to characterize for some types of trials, particularly for trials of implantable cardioverter defibrillators (ICDs). Although these devices reduce sudden death, pump failure death may either be neutrally affected or increased. Data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT) suggest that ICD therapy is associated with a shift in risk from sudden death to a subsequent heart failure risk.[61]

Challenges associated with defining events

Heart failure as a complication of other conditions

Heart failure may occur as a result of other disease processes, such as MI, atrial fibrillation, or pulmonary disease, or heart failure may be exacerbated by these diseases. It is difficult to determine the classification priority when these events occur simultaneously. Adjudication committees are often very helpful in these circumstances.

Defining the syndrome: systolic vs. diastolic heart failure

Defining heart failure events is uniquely challenging in patients with diastolic heart failure or heart failure with preserved systolic function (HF-PSF). In patients with impaired left ventricular function, majority of hospitalizations is attributable to heart failure. However, non-cardiovascular causes of hospitalization and death are common in patients with HF-PSF. These patients have many comorbidities including atrial fibrillation, anemia, renal dysfunction,

pulmonary disease, cerebrovascular disease, and depression.[62] Thus, a more stringent heart failure event definition may be needed in these patients to ensure accurate and relevant event classification. Echocardiography may also be useful in this setting to document diastolic dysfunction.[63]

Developing a meaningful event definition

Heart failure events in clinical trials should be defined in a clinically meaningful way such that they are relevant to clinicians, regulators, and patients. Hospitalization is generally always clinically relevant for both physicians and patients. Using symptoms to define heart failure may be more challenging, because symptoms such as dyspnea, although clinically relevant, can be non-specific for heart failure. Using non-specific criteria to classify heart failure events may be more problematic in non-heart failure cardiovascular clinical trials than in heart failure trials, where worsening dyspnea is more likely to represent heart failure. In heart failure trials, the need for intravenous vasoactive or diuretic therapy is often a component of the heart failure event definition. Creating a definition of this nature may identify a more severe heart failure event, but other less severe heart failure events may remain undetected. Emergency department admissions have been used to define heart failure events in some trials, and it may be an important component of the definition, particularly if assessments of resource utilization are of interest.

It is impractical to create a heart failure definition that is clinically relevant and satisfies all types of trials across multiple disciplines. However, it may be feasible to propose a standard, uniform set of criteria that would provide the framework to define heart failure across trials. This definition could be used across all non-heart failure cardiovascular clinical trials and heart failure trials where appropriate. Additional uniform definition components could be added to this standard heart failure event definition in heart failure trials as needed to address specific issues related to the intervention or the severity of disease in the population under study. We propose that a consensus definition should address the following concepts: (i) objective evidence of cardiac dysfunction (e.g. cardiac imaging, BNP) and that the patient has and is receiving treatment for heart failure; (ii) the event is clinically meaningful; (iii) the event captures the course of the disease; (iv) the event is acceptable to regulatory bodies. Hospitalization should be included in the definition.

The meeting participants developed a set of definitions for heart failure. These include new onset heart failure as a diagnosis in patients without known heart failure enrolled in non-heart failure trials, heart failure as a new event in patients with no previously known heart failure, and heart failure as an event in patients with known heart failure enrolled in non-heart failure trials (see Supplementary material online, *Table S3*). Investigators may adapt this proposed definition to meet the needs of a particular clinical trial. In some trials, a more stringent definition may be desired and all of the proposed components may be applied. For other trials, a less stringent definition may be appropriate and only specific aspects of the definitions may be used. These definitions are intended to be a framework that may be adapted to the circumstances of the clinical trial and study population. Of course, the definition should be included in the trial protocol, and the definition used should be reported explicitly in the trial report to facilitate interpretation of the heart failure results. These definitions also provide an opportunity for research. Data collected in clinical trials may be tested against these definitions to validate them and to determine the prognosis of patients identified as having new onset heart failure. These definitions may be continually refined as needed, as experience using them accumulates.

Several areas where further discussion is needed before a consensus can be reached include: (i) development of a method to avoid or minimize confounding by variations in practice when heart failure events are defined by hospitalizations and/or treatment interventions; (ii) assessment of events in the context of comorbidities; (iii) determination of whether adjudication committees are necessary to evaluate heart failure events in all major trials or whether more robust case report forms and protocols are adequate to evaluate events. We put forth definitions for further consideration by the cardiovascular clinical trial community.

Conclusion

Heart failure is a frequent event in cardiovascular non-heart failure trials. It is also a serious event associated with poor outcome. It is a complex clinical event represented by a variety of signs and symptoms. The symptom assessment is often subjective; thus, similar symptoms may be described differently in individual patients. In addition, the pathophysiology is heterogeneous, making precipitating factors difficult to ascertain in some patients. Despite these challenges, a consistent approach to defining heart failure events in cardiovascular clinical trials is needed. In the absence of a consensus definition, clinical trial data may not reliably describe the occurrence of heart failure events, the effect of treatment on heart failure events, or the differentiation between heart failure and non-heart failure events.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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